Application No. 09/937,191
Filed: January 3, 2002
TC Art Unit: 1642
Confirmation No.: 6276

REMARKS

In response to the restriction requirement, Applicant elects Group 16, drawn to use of CD13 inhibitor. This election is made with traverse. Regarding the second genus noted by the Examiner, claims 3 and 22, drawn to utilization wherein the immune diseases are autoimmune diseases or rejections of transplanted organs or allergies, have been cancelled.

The Examiner states that the pending claims of the above-referenced patent application do not relate to a single inventive concept because claim 1 is not novel and lacks an inventive step when compared to WO98/44923. Therefore, the Examiner has divided the claims into 60 restriction groups. This restriction requirement is respectfully traversed for the following reasons, and reconsideration is requested.

Amended claim 1 defines the use of an aminopeptidase inhibitor for the treatment of very early stages of tumor diseases wherein the treated tumor is a primary tumor and whereby the inhibitor causes blocking of polarization of invasive tumor cells (metastasis). Claims 2, 4-8, 16, 21 and 23-26 are dependent upon claim 1. Amended independent claims 9 and 12 are directed to methods of identifying the appropriate inhibitors, which can be used in the use as claimed in claim 1.

Page 1 of the specification describes suitable aminopeptidase inhibitors as including actinoin, bestatin and homophthalimide type inhibitors. The Applicant has discovered that aminopeptidase inhibitors interfere with cell polarization mechanisms operating in tumor diseases. Cell polarization is the mechanism by which tumor cells elongate from a spherical state to a migratory state.

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As a direct consequence of Applicant's recognition of this mechanism, Applicant can now teach that aminopeptidase inhibitors are useful for the treatment of the very early stages of tumor diseases wherein the tumor is a primary tumor. Furthermore, Applicant can also teach that aminopeptidase inhibitors are not useful, and in fact are harmful, for the treatment of the later stages of tumor diseases wherein the tumor has metastasized. In contrast, WO98/44923 discloses the use of the aminopeptidase inhibitor actinonin for treating neoplastic cells in general (page 5, line 18, to page 6, line 7, claims), making no distinction as to the importance of the timing of the use of this inhibitor. WO98/44923 neither discloses nor suggests that aminopeptidase inhibitors interfere with cell polarization or are particularly useful when used in the treatment of very early stages of tumor diseases wherein that treated tumor is a primary tumor.

The recognition by the Applicant that aminopeptidase inhibitors do interfere with cell polarization as their mechanism of operation in the control of tumor diseases is highly relevant for determining the correct presenting indication for the proper clinical, therapeutic use of these inhibitors. Cell polarization is the mechanism by which tumor cells elongate from a spherical state to a migratory state. The Applicant has clearly documented in the instant application that the aminopeptidase inhibitors interfere with cell polarization and thereby prevent tumor cells from reaching a migratory state, necessary for metastasis. However, when the aminopeptidase inhibitor is applied to later stage tumors, e.g., when the cell has formed a long axis and thus has formed the migratory phenotype, the inhibition of aminopeptidase dramatically enhances the speed of cell migration

by up to a factor 50, completely opposite to what is desired for a therapeutic effect.

Therefore, it is necessary to apply therapeutic aminopeptidase inhibitors in the very early stages of tumor diseases (before metastasis), when few cells try to evade the primary tumor by starting the process of polarization. In the same vein, it is very dangerous to apply these agents to treat tumors that have already formed metastases, because this stage is characterized by an all over migration of tumor cells. The data of the Applicant clearly indicate that the use of aminopeptidase inhibitors would be deleterious, and in fact dangerous for patients in the later stages of tumor diseases. These agents actually accelerate the formation of metastases by speeding up tumor cell migration.

In the Examples, the Applicant documents that aminopeptidases are a kind of a brake and belong to the intrinsic machinery of cell migration, modifying the shape of the cell and slowing down the migration speed by regulation of the interplay between focal adhesion and loss of adhesion. Aminopeptidase inhibitors block this fine tuning machinery. Therefore, Applicant's data indicate a beneficial use of these inhibitors (alone or in combination with other drugs) in the early stages of tumor diseases, while, in contrast, a deleterious effect can be expected in more progressed stages of disease. These distinctions, now incorporated in the Applicant's claims, are clearly based upon the above-described intrinsic cellular mechanisms.

The Applicant's observations and discoveries are supported by the results of others of skill in the art. Aminopeptidase is a metalloproteinase. There is overwhelming evidence from current

international cancer trials indicating that the use of anti-metalloproteinases in cancer may lead to an "explosion" of tumors. Hence, all these trials have been stopped recently because of these unexpected results. Actually, the rational basis of these trials was that metalloproteinases are used by tumor cells to degrade the extracellular matrix proteins to facilitate invasion so that inhibition would act against the mechanism. This assumption has turned out not to be correct. In contrast, Applicant's results strongly rule out the use of these drugs at stages when the tumors have already formed metastases (evidence of the migratory phenotype). This recognition is a new insight that is based on Applicant's technology and that cannot be derived from the known prior art documents.

Therefore, the subject matter of amended claims 1, 9 and 12 should be considered not only novel, but also as inventive. The restriction requirement is, therefore, improper. Newly amended claims 1, 9 and 12, and the claims dependent thereon, should therefore be recognized as allowable.

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The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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BEH/dkh/308059